REMARKS

Reconsideration and allowance of all pending claims (claims 16, 19, 22, 24-26) are respectfully requested. Applicants address each of the rejections of the January 25, 2005 Office Action, as follows.

Priority

Applicants have amended the specification show that prior non-provisional application Serial No. 08/624,469, filed May 10, 1996 was abandoned.

Specification

Applicants have amended the specification by the addition of the abstract section. Support may be found, for example, on page 1, lines 4-10.

Claims 16-26 Stand Rejected for Lack of Written Description

Reconsideration and withdrawal of the rejection of claims 16-26 for lack of written description under 35 U.S.C. 112, first paragraph, are respectfully requested. The rejection spanning pages 3-7 of the Office Action essentially states that the claims, prior to the present amendment, failed to provide any structural information relating to the recited nucleotide sequences. With the entry of the instant amendment, Applicants believe that they have overcome this rejection.

Claims 16 and 19 now recite that the nucleic acid encodes: the p53 Val135 mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro* (which the Examiner admits in the last sentence of page 3 spanning page 4 of the Office Action has sufficient support in the specification); the binding site of p53 consisting of SEQ ID NO:2; or SEQ ID NO:1 that encodes an antisense RNA that inhibits expression of p53. Hence, the claims now provide the critical structures of the nucleic acids that the Examiner previously argued were lacking.

Claim 22 and dependent claims thereof have been amended to recite one type of activity, i.e., the activity observed in Example 2 of the specification wherein toxicity of cultured neuronal cells is reduced by the administration of an antisense RNA which inhibits expression of p53, and in particular, the antisense RNA consisting of SEQ ID NO:1.

Claims 16-26 Stand Rejected for Lack of Enablement

Claims 16-26 stand rejected under 35 U.S.C 112, first paragraph, as encompassing broader constructs and methods than one of skill in the art would be enabled by the disclosure of the specification to make and use. Reconsideration and withdrawal of this rejection are respectfully requested.

Applicants have amended pending claims16 and 19 to recite that the recombinant virus is selected from the group consisting of adenovirus, adeno-virus and herpes virus wherein said recombinant virus comprises a nucleic acid selected from the group consisting of (a) a DNA encoding the p53 Val135 mutate form of p53; (b) a DNA comprising a binding site for p53, wherein the DNA consists of SEQ ID NO:2; and (c) a nucleic acid encoding an antisense RNA consisting of SEQ ID NO:1 which inhibits expression of p53.

Furthermore, Applicants have amended pending methods claims 22, and 23-26 to recite a method of inhibiting toxicity of neuronal cells in culture by administering an nucleic acid encoding an antisense RNA which inhibits expression of p53 consisting of SEQ ID NO: 1.

Applicants submit that the amendments made herein overcome the enablement rejection.

Claims 16-26 Stand Rejected As being Indefinite

The rejection made under 35 U.S.C 112, second paragraph is believed to be moot by the entry of the instant amendment to the claims.

Claims 16, 17 and 20 Stand Rejected under 35 U.S.C. 102(e)

Claims 16, 17 and 20 stand rejected under 35 U.S.C. 102(e) as being anticipated by Roth et al (US 6,017,524) as evident by Chatterjee et al (US 5,474,935). Applicants submit that amended claim 16 is not anticipated by Roth because the reference does not teach the specific antisense RNA having the sequence of SEQ ID NO:1 as claimed by Applicants. Claims 17 and 20 are cancelled. Accordingly, Applicants submit that this rejection has been overcome and respectfully request withdrawal of the rejection.

Claims 16, 17 and 20 Stand Rejected under 35 U.S.C. 103(a)

Claims 16, 17 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5,087,617) taken with Roth et al (US 6,017,524), Srivastava (US 6,261,834), Levrero et al

(Gene, 1991) or Kufe et al (US 5,565,334) . Applicants traverse this rejection for the following reasons.

Claim 16 and dependent claim 19 are the only product claims now pending in this application. In order to render claim 16 (and dependent claim 19) unpatentable under U.S.C. 103(a), the combination of references must teach or disclose every element of the claimed invention. See M.P.E.P. § 2142. Furthermore, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or combine reference teachings. See M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *Id.*

Smith discloses a method for depleting or substantially depleting bone marrow of malignant cells by exposing said cells with oligonucleotides such as antisense p53 oligonucleotides under conditions that facilitate their uptake by the malignant cells. This is accomplished by the simple incubation of the cells with the oligonucleotides in a suitable nutrient medium for a period of time. (See column 10, lines 29-33). Applicants contend that the Smith primary reference does not disclose in column 5 "a plasmid encoding antisense p53 RNA", but instead discloses antisense p53 oligonucleotides free of being incorporated into a plasmid or the like contained within a viral vector as Applicants' claimed invention requires. Applicants further submit that even in combination with the secondary references described below, the instant claimed invention is not taught nor suggested.

Roth et al teaches the preparation of retroviral vectors, and contemplates the use of other vectors such as adenovirus and adeno-associated virus for the preparation of recombinant viruses that p53 gene or antisense p53 gene. Absent in the Roth reference is a teaching of viral vectors such as herpes virus or that the antisense p53 gene must consist of SEQ ID NO:1 or that the p53 gene must consist of the mutant p53 Val135 p53.

Srivastava is cited by the Examine for teaching the use of recombinant adeno-associate virus comprising heterologous genes encoding antisense RNA. No where in this reference is there a teaching or suggestion that would motivate one skilled in the art to make a claimed recombinant viruses containing the recited specific nucleic acid sequences for the purpose inhibiting p53 protein-mediated toxicity in cultured neuronal cells.

Leveror is cited for the general teaching of recombinant defective adenoviruses for harboring foreign nucleic acids *in vitro*. Similar to the argument made above, there is no explanation why one would be motivated to use the recombinant defective adenoviruses described by Leveror to make the specific recombinant adenovirus claimed by Applicants that contains SEQ ID NO:1, SEQ ID NO:2 or p53 Val135 mutated p53.

Kufe is cited for the teaching of gene delivery systems for targeting cells. Once again, there is no motivation why one would want to make any of these delivery systems to make the specific recombinant adenovirus claimed by Applicants that contains SEQ ID NO:1, SEQ ID NO:2 or p53 Val135 mutated p53.

Because none of the references relied upon teach or suggest the claimed recombinant virus or claimed method, Applicants request the withdrawal of this rejection.

Claims 16, 18 and 20 Stand Rejected under 35 U.S.C. 103(a)

Claims 16, 18 and 20 stand rejected under 35 U.S.C. 102(a) as being unpatentable over Funk et al taken with Srivastava, Levrero or Kufe. Applicants respectfully traverse this rejection.

According to the Office Action, Funk et al discloses a DNA binding site for p53 identical to SEQ ID NO:2 but lacks a teaching of recombinant viruses consisting of adenovirus, adeno-associated virus, and herpes virus that contain SEQ ID NO: 2. Srivastava, Levrero and Kufe are cited to demonstrate this knowledge at the time of the claimed invention. According to the Examiner, Funk's disclosure of a binding site identical to SEQ ID NO: 2 renders obvious a recombinant virus comprising SEQ ID NO:2 because the secondary references teach one how to generally prepare viral vectors.

However, Applicants submit that Funk does not teach or suggest that DNA binding sites for p53 consisting of SEQ ID NO:2 should be incorporated into recombinant viruses for any purpose. Funk only sets forth the nucleic acid sequence SEQ ID NO:2. The secondary references have been described and distinguished in the previous rejection above. There is no motivation in Funk alone or in combination with the secondary references why one skilled in the art should make recombinant viruses comprising SEQ ID NO:2. The simple fact that SEQ ID NO:2 was disclosed by Funk does not render obvious recombinant viruses containing and expressing SEQ ID NO:2, unless there is motivation to do so. Without this nexus, Applicants submit that the rejection is improper. Because none of the references relied upon teach or suggest the claimed recombinant virus, Applicants request withdrawal of this rejection.

Claims 16, 20 and 21 Stand Rejected under 35 U.S.C. 103(a)

Claims 16, 20 and 21 stand rejected under 35 U.S.C. 102(a) as being unpatentable over Michalovitz et al taken with Srivastav, Levrero et al or Kufe. The Examiner's reasoning is set forth on pages 223-23 of the Office Action. Applicants traverse this rejection for the following reason.

Michalovitz et al describes the effects of a temperature sensitive mutant p53 protein, in particular, p53val135, on rat embryo fibroblast cells. The reference is silent as to the making and expression of the mutant p53 in recombinant viruses such as herpes, adenovirus or adeno-associted virus. The Examiner employs the secondary references of Srivastav, Leverero and Kufe to cure this deficiency.

Claim 16 and dependent claim 19 are the only product claims now pending in this application. In order to render claim 16 (and dependent claim 19) unpatentable under U.S.C. 103(a), the combination of references must teach or disclose every element of the claimed invention. See M.P.E.P. § 2142. Furthermore, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or combine reference teachings. See M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *Id.*

In a similar argument as made previously, Michalovitz et al does not teach or suggest that p53Val135 be incorporated into recombinant viruses. Michalovitz et al only sets forth plasmids containing p53Val135 for a purpose completely different than Applicants'. Although the claimed invention are product claims and little weight is given to an intended use (as the Examiner states on page 22 of the Office Action), there is no motivation in Michalovitz or the secondary references to combine them to make recombinant viruses that express p53Val135. The simple fact that p53Val135 was disclosed by Michaloviz does not render obvious recombinant viruses containing and expressing p53Val135, unless there is motivation to do so. Without this nexus, Applicants submit that the rejection is improper. Because none of the references relied upon teach or suggest the claimed recombinant virus, Applicants request withdrawal of this rejection.

Applicants respectfully submit that the application is now in condition for allowance and request prompt notice thereof.

Respectfully submitted,

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